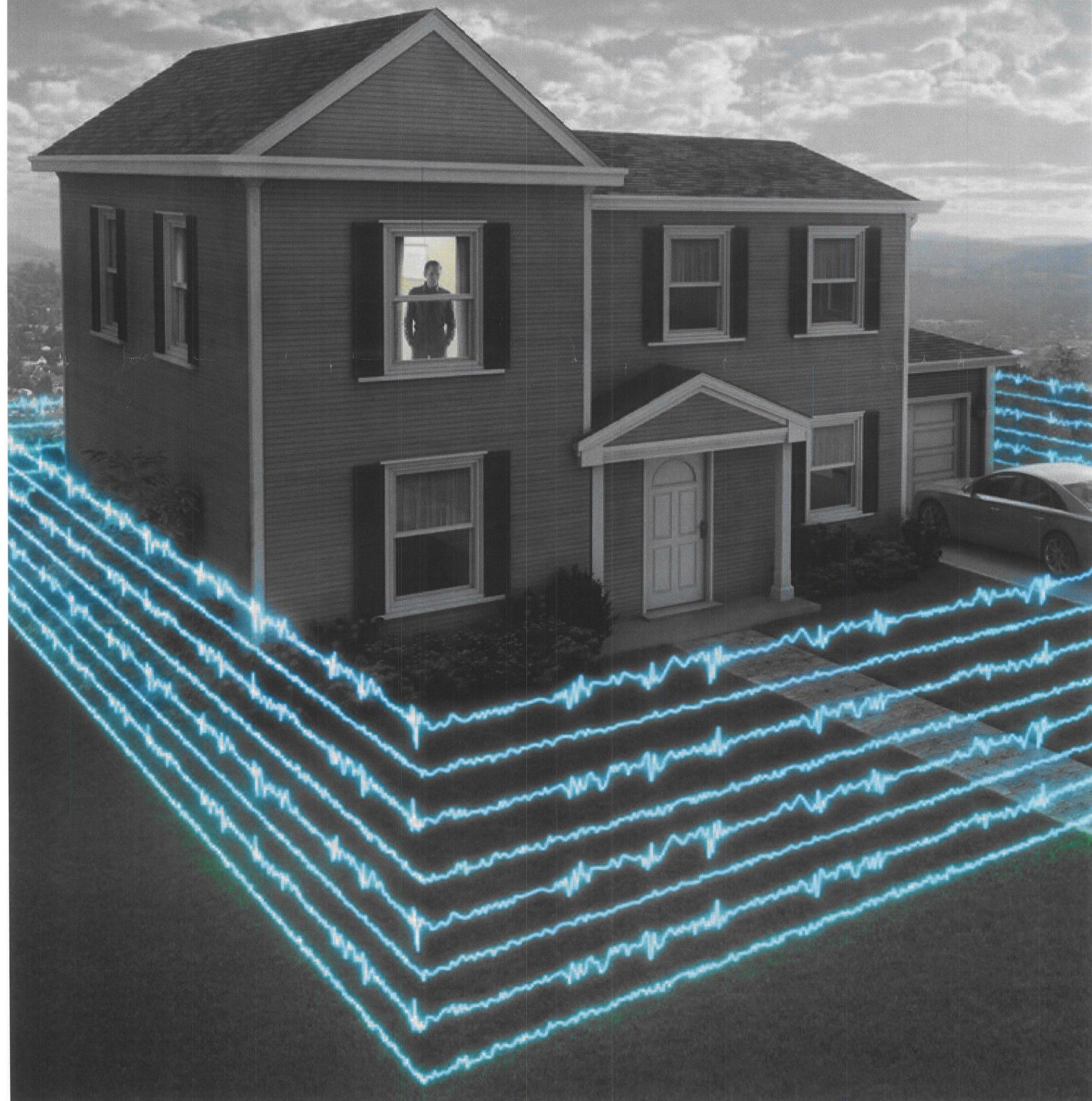


SEIZURES CAN KEEP PATIENTS FEELING CONFINED



For the adjunctive treatment of partial-onset seizures

PUT PATIENTS ON A PATH TO POWERFUL SEIZURE REDUCTION

Learn more about APTIOM
at AES Booth 105

- Reduce seizure frequency with once-daily Aptom® (eslicarbazepine acetate)
- Significant reduction in seizure frequency in 3 randomized, double-blind, placebo-controlled studies^{*†}
- Incidences of aggression and agitation comparable to placebo²
- In most patients, titration is 1 step, 1 week to the recommended maintenance dose¹
 - May be taken either whole or crushed, with or without food¹

Indication and Usage

APTIOM is indicated as adjunctive treatment of partial-onset seizures.

Important Safety Information for APTIOM

- **Contraindications:** APTIOM is contraindicated in patients with a hypersensitivity to eslicarbazepine acetate or oxcarbazepine.
- **Suicidal Behavior and Ideation:** Antiepileptic drugs (AEDs), including APTIOM, increase the risk of suicidal thoughts or behavior. Anyone considering prescribing APTIOM or any other AED must balance this risk with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. Patients and caregivers should also be advised to be alert to these behavioral changes and to immediately report them to the healthcare provider.
- **Serious Dermatologic Reactions,** including Stevens-Johnson Syndrome (SJS), have been reported in association with APTIOM use. Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and SJS, have been reported in patients using oxcarbazepine or carbamazepine, which are chemically related to APTIOM. Should a patient develop a dermatologic reaction while using APTIOM, discontinue APTIOM use unless it is clearly not drug related.
- **Adverse Reactions:** The most frequently reported adverse reactions in patients receiving APTIOM at doses of 800 mg or 1200 mg ($\geq 4\%$ and $\geq 2\%$ greater than placebo) were dizziness, somnolence, headache, diplopia, vomiting, fatigue, vertigo, ataxia, blurred vision, and tremor.

***Study design:** Three studies, each consisting of 8-week baseline, 2-week titration, and 12-week maintenance phases, established the efficacy of APTIOM in patients with partial-onset seizures not adequately controlled with 1–3 AEDs. The standardized seizure frequency during the maintenance phase over 28 days was the primary endpoint. APTIOM 400 mg/day was evaluated in Studies 1 and 2 and did not show significant treatment effect. Treatment effects were statistically significant with APTIOM 800 mg/day in Studies 1 and 2, but not in Study 3, and with APTIOM 1200 mg in all 3 studies.¹



learn more at
www.AptomHCP.com/info

Please see additional
Important Safety Information
and Brief Summary of Prescribing
Information on adjacent pages.

For the adjunctive treatment of partial-onset seizures

PUT PATIENTS ON A PATH TO POWERFUL SEIZURE REDUCTION



Indication and Usage

Aptiom® (eslicarbazepine acetate) is indicated as adjunctive treatment of partial-onset seizures.

Important Safety Information for APTIOM

Contraindications: APTIOM is contraindicated in patients with a hypersensitivity to eslicarbazepine acetate or oxcarbazepine.

Suicidal Behavior and Ideation: Antiepileptic drugs (AEDs), including APTIOM, increase the risk of suicidal thoughts or behavior. Anyone considering prescribing APTIOM or any other AED must balance this risk with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. Patients and caregivers should also be advised to be alert to these behavioral changes and to immediately report them to the healthcare provider.

Serious Dermatologic Reactions, including Stevens-Johnson Syndrome (SJS), have been reported in association with APTIOM use. Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and SJS, have been reported in patients using oxcarbazepine or carbamazepine, which are chemically related to APTIOM. Should a patient develop a dermatologic reaction while using APTIOM, discontinue APTIOM use unless it is clearly not drug related.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as Multiorgan Hypersensitivity, has been reported in patients taking APTIOM. DRESS typically, although not exclusively, presents with fever, rash, and/or lymphadenopathy, in association with other organ system involvement. If this reaction is suspected, treatment with APTIOM should be discontinued.

Anaphylactic Reactions and Angioedema: Rare cases of anaphylaxis and angioedema have been reported in patients taking APTIOM. Anaphylaxis and angioedema associated with laryngeal edema can be fatal. If a patient develops any of these reactions, the drug should be discontinued. Patients with a prior anaphylactic-type reaction after treatment with either oxcarbazepine or APTIOM should not be treated with APTIOM.

Hyponatremia: Clinically significant hyponatremia (sodium <125 mEq/L) can develop in patients taking APTIOM. In the controlled epilepsy trials, 1.0% (800 mg) and 1.5% (1200 mg) of patients treated with APTIOM had at least one serum sodium level value less than 125 mEq/L, compared to none on placebo. These effects were dose related and generally appeared within the first 8 weeks of treatment (as early as after 3 days). Measurement of serum sodium and chloride levels should be considered during maintenance treatment with APTIOM, particularly if the patient is receiving other medications known to decrease serum sodium levels.

Neurological Adverse Reactions: APTIOM causes dose-dependent increases in the following reactions (dizziness, disturbance in gait and coordination, somnolence, fatigue, cognitive dysfunction, and visual changes) compared to placebo. These events were more often serious in

APTIOM-treated patients than placebo. There was an increased risk of dizziness, disturbance in gait and coordination, and visual changes during the titration period (compared to the maintenance period), and there may be an increased risk of these adverse reactions in patients 60 years of age and older compared to younger adults. The incidences of dizziness and diplopia were greater with concomitant use of APTIOM and carbamazepine compared to the use of APTIOM without carbamazepine. Prescribers should advise patients against engaging in hazardous activities requiring mental alertness, such as operating motor vehicles or dangerous machinery, until the effect of APTIOM is known.

Withdrawal of AEDs: As with all AEDs, APTIOM should be withdrawn gradually because of the risk of increased seizure frequency and status epilepticus.

Drug Induced Liver Injury: Hepatic effects, ranging from mild to moderate elevations in transaminases (>3 times the upper limit of normal) to rare cases with concomitant elevations of total bilirubin (>2 times the upper limit of normal) have been reported with APTIOM use. Baseline evaluations of liver laboratory tests are recommended. APTIOM should be discontinued in patients with jaundice or other evidence of significant liver injury.

Abnormal Thyroid Function Tests: Dose-dependent decreases in serum T3 and T4 (free and total) values have been observed in patients taking APTIOM. These changes were not associated with other abnormal thyroid function tests suggesting hypothyroidism. Abnormal thyroid function tests should be clinically evaluated.

Adverse Reactions: The most frequently reported adverse reactions in patients receiving APTIOM at doses of 800 mg or 1200 mg ($\geq 4\%$ and $\geq 2\%$ greater than placebo) were dizziness, somnolence, nausea, headache, diplopia, vomiting, fatigue, vertigo, ataxia, blurred vision, and tremor.

Dosing Considerations

When APTIOM and carbamazepine are taken concomitantly, the dose of APTIOM or carbamazepine may need to be adjusted based on efficacy and tolerability. APTIOM should not be taken as an adjunctive therapy with oxcarbazepine. For patients taking other enzyme-inducing AEDs (i.e., phenobarbital, phenytoin, and primidone), higher doses of APTIOM may be needed.

A dose reduction is recommended in patients with moderate and severe renal impairment (i.e., creatinine clearance <50 mL/min).

Dose adjustments are not required in patients with mild to moderate hepatic impairment. Use of APTIOM in patients with severe hepatic impairment has not been studied, and use in these patients is not recommended.

Concomitant use of APTIOM and oral contraceptives containing ethinylestradiol and levonorgestrel is associated with lower plasma levels of these hormones. Patients should use additional or alternative non-hormonal birth control during APTIOM treatment and after discontinuation of APTIOM for one menstrual cycle, or until otherwise instructed.

Please see Brief Summary of Full Prescribing Information on adjacent pages.

References: 1. APTIOM [prescribing information]. Sunovion Pharmaceuticals Inc., Marlborough, MA, November 2013. 2. Data on file, Sunovion Pharmaceuticals Inc.

 **SUNOVION**

Under license from 

* is a registered trademark of Sumitomo Dainippon Pharma Co., Ltd.
Sunovion Pharmaceuticals Inc., is a U.S. subsidiary of Sumitomo Dainippon Pharma Co., Ltd.
©2014 Sunovion Pharmaceuticals Inc. All rights reserved. 10/14 APT527-14

ONCE DAILY
Aptiom®
(eslicarbazepine acetate) tablets
200 mg • 400 mg • 600 mg • 800 mg

BRIEF SUMMARY OF FULL-PREScribing INFORMATION

INDICATIONS AND USAGE

Partial-Onset Seizures
 Aptiom (eslicarbazepine acetate) is indicated as adjunctive treatment of partial-onset seizures.

CONTRAINDICATIONS

Aptiom is contraindicated in patients with a hypersensitivity to eslicarbazepine acetate or oxcarbazepine.

WARNINGS AND PRECAUTIONS

Suicidal Behavior and Ideation
 Antiepileptic drugs (AEDs), including Aptiom, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% confidence interval [CI]: 1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior per 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number of events is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5–100 years) in the clinical trials analyzed.

Table 2 shows absolute and relative risk by indication for all evaluated AEDs.

Table 2: Risk of Suicidal Thoughts or Behavior by Indication for Antiepileptic Drugs in the Pooled Analysis

Indication	Placebo Patients with Events Per 1000 Patients	Drug Patients with Events Per 1000 Patients	Risk Difference: Additional Drug Patients/Incidence in Placebo Patients
Epilepsy	1.0	3.4	3.5
Psychiatric	5.7	8.5	1.5
Other	1.0	1.8	1.9
Total	2.4	4.3	1.8

The relative risk for suicidal thoughts or behavior was higher in clinical trials in patients with epilepsy than in clinical trials in patients with psychiatric or other conditions, but the absolute risk differences were similar for epilepsy and psychiatric indications.

Anyone considering prescribing Aptiom or any other AED must balance this risk with the risk of untreated illness. Epilepsy and many other illnesses for which

including seizures, severe nausea/vomiting leading to dehydration, severe gait instability, and injury. Some patients required hospitalization and discontinuation of Aptiom. Concurrent hypochloremia was also present in patients with hyponatremia. Depending on the severity of hyponatremia, the dose of Aptiom may need to be reduced or discontinued.

Neurological Adverse Reactions
 Measurement of serum sodium and chloride levels should be considered during maintenance treatment with Aptiom, particularly if the patient is receiving other medications known to decrease serum sodium levels and should be performed if symptoms of hyponatremia develop (e.g., nausea/vomiting, malaise, headache, lethargy, confusion, irritability, muscle weakness/spasms, obtundation, or increase in seizure frequency or severity).

Drug-Induced Liver Injury
 Hepatic effects, ranging from mild to moderate elevations in transaminases (>3 times the upper limit of normal) to rare cases with concomitant elevations of total bilirubin (>2 times the upper limit of normal) have been reported with Aptiom use. Baseline evaluations of liver laboratory tests are recommended. The combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury. Aptiom should be discontinued in patients with jaundice or other evidence of significant liver injury (e.g., laboratory evidence).

Abnormal Thyroid Function Tests
 Dose-dependent decreases in serum T₃ and T₄ (free and total) values have been observed in patients taking Aptiom. These changes were not associated with other abnormal thyroid function tests suggesting hypothyroidism. Abnormal thyroid function tests should be clinically evaluated.

ADVERSE REACTIONS
Clinical Trials Experience
 Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In all controlled and uncontrolled trials in patients with partial-onset seizures, 1195 patients received Aptiom of whom 586 were treated for longer than 6 months and 462 for longer than 12 months. In the placebo controlled trials in patients with partial-onset seizures, 1021 patients received Aptiom. Of the patients in those trials, approximately 95% were between 18 and 60 years old, approximately 50% were male, and approximately 80% were Caucasian.

Adverse Reactions Leading to Discontinuation
 In the controlled epilepsy trials (Studies 1, 2, and 3), the rate of discontinuation as a result of any adverse reaction was 14% for the 800 mg dose, 25% for the 1200 mg dose, and 7% in subjects randomized to placebo. The adverse reactions most commonly ($\geq 1\%$ in any Aptiom treatment group, and greater than $\geq 2\%$ in placebo) leading to discontinuation, in descending order of frequency, were dizziness, nausea, vomiting, ataxia, diplopia, somnolence, headache, blurred vision, vertigo, asthenia, fatigue, rash, dysarthria, and tremor.

Most Common Adverse Reactions
 The most frequently reported adverse reactions in patients receiving Aptiom at doses of 800 mg or 1200 mg ($\geq 4\%$ and $\geq 2\%$ greater than placebo) were dizziness, somnolence, nausea, headache, diplopia, vomiting, fatigue, vertigo, ataxia, blurred vision, and tremor. Table 3 gives the incidence of adverse reactions that occurred in $\geq 2\%$ of subjects with partial-onset seizures in any Aptiom treatment group and for which the incidence was greater than placebo during the controlled clinical trials. Adverse reactions during titration were less frequent for patients who began therapy at an initial dose of 400 mg for 1 week and then increased to 800 mg compared to patients who initiated therapy at 800 mg.

(and 0.2% of placebo-treated patients). There was an increased risk of these adverse reactions during the titration period (compared to the maintenance period) and also in patients 60 years of age and older (compared to younger adults). The incidence of diplopia was greater with the concomitant use of Aptiom and carbamazepine compared to the use of Aptiom without carbamazepine (up to 16% vs. 6%, respectively).

Hazardous Activities

Prescribers should advise patients against engaging in hazardous activities requiring mental alertness, such as operating motor vehicles or dangerous machinery, until the effect of Aptiom is known.

Withdrawal of AEDs

As with all antiepileptic drugs, Aptiom should be withdrawn gradually because of the risk of increased seizure frequency and status epilepticus.

Drug-Induced Liver Injury
 Hepatic effects, ranging from mild to moderate elevations in transaminases (>3 times the upper limit of normal) to rare cases with concomitant elevations of total bilirubin (>2 times the upper limit of normal) have been reported with Aptiom use. Baseline evaluations of liver laboratory tests are recommended. The combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury. Aptiom should be discontinued in patients with jaundice or other evidence of significant liver injury (e.g., laboratory evidence).

Abnormal Thyroid Function Tests
 Dose-dependent decreases in serum T₃ and T₄ (free and total) values have been observed in patients taking Aptiom. These changes were not associated with other abnormal thyroid function tests suggesting hypothyroidism. Abnormal thyroid function tests should be clinically evaluated.

ADVERSE REACTIONS
Clinical Trials Experience
 Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In all controlled and uncontrolled trials in patients with partial-onset seizures, 1195 patients received Aptiom of whom 586 were treated for longer than 6 months and 462 for longer than 12 months. In the placebo controlled trials in patients with partial-onset seizures, 1021 patients received Aptiom. Of the patients in those trials, approximately 95% were between 18 and 60 years old, approximately 50% were male, and approximately 80% were Caucasian.

Adverse Reactions Leading to Discontinuation
 In the controlled epilepsy trials (Studies 1, 2, and 3), the rate of discontinuation as a result of any adverse reaction was 14% for the 800 mg dose, 25% for the 1200 mg dose, and 7% in subjects randomized to placebo. The adverse reactions most commonly ($\geq 1\%$ in any Aptiom treatment group, and greater than $\geq 2\%$ in placebo) leading to discontinuation, in descending order of frequency, were dizziness, nausea, vomiting, ataxia, diplopia, somnolence, headache, blurred vision, vertigo, asthenia, fatigue, rash, dysarthria, and tremor.

Most Common Adverse Reactions
 The most frequently reported adverse reactions in patients receiving Aptiom at doses of 800 mg or 1200 mg ($\geq 4\%$ and $\geq 2\%$ greater than placebo) were dizziness, somnolence, nausea, headache, diplopia, vomiting, fatigue, vertigo, ataxia, blurred vision, and tremor. Table 3 gives the incidence of adverse reactions that occurred in $\geq 2\%$ of subjects with partial-onset seizures in any Aptiom treatment group and for which the incidence was greater than placebo during the controlled clinical trials. Adverse reactions during titration were less frequent for patients who began therapy at an initial dose of 400 mg for 1 week and then increased to 800 mg compared to patients who initiated therapy at 800 mg.

Table 3: Adverse Reactions Incidence in Pooled Controlled Clinical Trials of Adjunctive Therapy in Adults (Events $\geq 2\%$ of Patients in the Aptiom 800 mg or 1200 mg Dose Group and More Frequent Than in the Placebo Group)

	Aptiom		
	Placebo (N=126)	800 mg (N=415)	1200 mg (N=110)
Eye disorders	<1	2	6
Diplopia	2	9	11
Blurred vision	1	6	5
Vertigo	1	2	1
Ear and labyrinth disorders	1	2	1
Visual impairment	1	2	1
Gastrointestinal disorders	5	10	16
Nausea	5	10	16
Vomiting	3	6	10
Diarrhea	3	4	2
Constipation	1	2	2
Abdominal pain	1	2	2
Gastritis	<1	2	<1
General disorders and administration site conditions	4	4	7
Fatigue	2	2	3
Asthenia	2	2	3
Gait disturbance	<1	2	2
Peripheral edema	1	2	1
Infections and infestations	1	2	2
Urinary tract infections	1	2	2
Injury, poisoning and procedural complications	1	3	1
Fall	1	3	1
Metabolism and nutrition disorders	2	2	2
Hyponatremia	<1	2	2
Nervous system disorders	9	20	28
Dizziness	8	11	18
Somnolence	9	13	15
Headache	2	4	6
Ataxia	2	3	3
Balance disorder	<1	1	2
Tremor	1	2	4
Dysarthria	0	1	2
Memory impairment	<1	1	2
Nystagmus	1	2	2
Psychiatric disorders	2	1	2
Depression	1	2	2
Insomnia	1	2	2
Respiratory, thoracic and mediastinal disorders	1	1	2
Cough	1	2	1
Skin and subcutaneous tissue disorders	1	2	1
Rash	1	1	3
Vascular disorders	1	1	2
Hypertension	1	1	2
Phenobarbital	1	1	1
Carbamazepine	1	1	1
Topiramate	1	1	2
Valproate	<1	1	1

*Potential pharmacokinetic interaction
 **Other adverse reactions with Aptiom use
 Compared to placebo, Aptiom use was associated with slightly higher frequencies of decreases in hemoglobin and hematocrit increases in total cholesterol, triglycerides, and LDL, and increases in creatine phosphokinase.

Adverse Reactions Based on Gender and Race
 No significant gender differences were noted in the incidence of adverse reactions. Although there were few non-Caucasian patients, no differences in the incidences of adverse reactions compared to Caucasian patients were observed.

DRUG INTERACTIONS

General Information
 Several AEDs (e.g., carbamazepine, phenobarbital, phenytoin, and primidone) can induce enzymes that metabolize Aptiom and can cause decreased plasma concentrations of eslicarbazepine (see Figure 1).

Aptiom can inhibit CYP2C19, which can cause increased plasma concentrations of drugs that are metabolized by this isoenzyme (e.g., phenytoin, clofazam, and omeprazole). *In vivo* studies suggest that Aptiom can induce CYP3A4, decreasing plasma concentrations of drugs that are metabolized by this isoenzyme (e.g., simvastatin) (see Figure 2).

Potential for Other AEDs to Affect Aptiom
 The potential impact of other AEDs on the systemic exposure (area under the curve, AUC) of eslicarbazepine, the active metabolite of Aptiom, is shown in Figure 1:

Figure 1: Potential Impact of Other AEDs on AUC of Aptiom
Eslicarbazepine

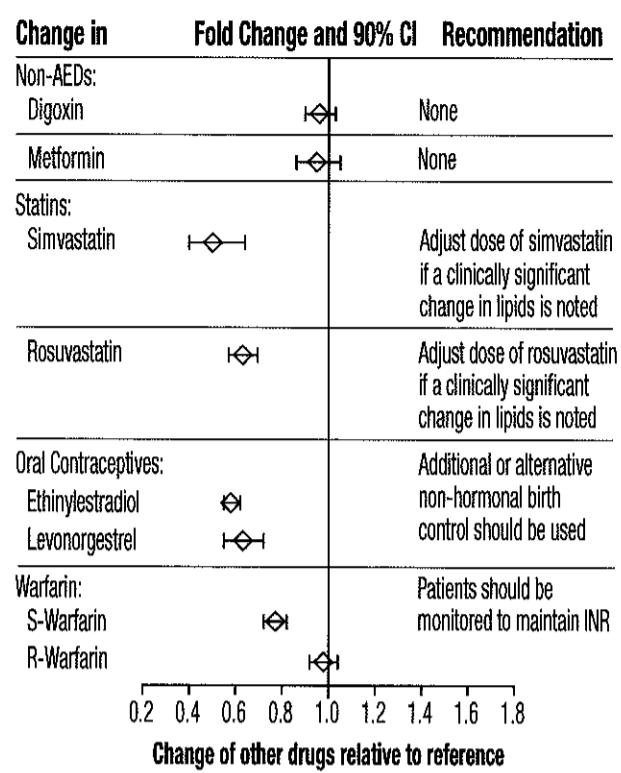
	Change due to Carbamazepine	Fold Change and 90% CI	Recommendation
Carbamazepine	↑	May need dose adjustment	
Gabapentin	↓	None	
Lamotrigine	↓	None	
Levetiracetam	↓	None	
Phenobarbital*	↑	May need higher dose of Aptiom	
Phenytoin	↑	May need higher dose of Aptiom	
Topiramate	↓	None	
Valproate	↓	None	

*Phenobarbital auto-inactivates like AEDs (e.g., primidone)

Potential for Aptiom to Affect Other Drugs
 The potential impact of Aptiom on the systemic exposure (AUC) of other drugs (including AEDs) is shown in Figure 2:

	Change in AUC of AEDs	Fold Change and 90% CI	Recommendation
Carbamazepine	↑	May need dose adjustment	
Gabapentin	↓	None	
Lamotrigine	↓	None	
Levetiracetam	↓	None	
Phenobarbital	↓	None	
Phenytoin	↑	Monitor plasma phenytoin concentration in epilepsy, dose adjustment may be needed based on clinical response and serum levels of phenyto	

Figure 2b: Potential Impact of APTIOM on the AUC of Non-AEDs



Oral Contraceptives

Because concomitant use of APTIOM and ethinylestradiol and levonorgestrel is associated with lower plasma levels of these hormones, females of reproductive potential should use additional or alternative non-hormonal birth control.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. In oral studies conducted in pregnant mice, rats, and rabbits, eslicarbazepine acetate demonstrated developmental toxicity, including teratogenicity (mice), embryolethality (rats), and fetal growth retardation, at clinically relevant doses. APTIOM should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

When eslicarbazepine acetate was orally administered (150, 350, 650 mg/kg/day) to pregnant mice throughout organogenesis, increased incidences of fetal malformations was observed at all doses and fetal growth retardation was observed at the mid and high doses. A no-effect dose for adverse developmental effects was not identified. At the lowest dose tested, plasma eslicarbazepine exposure (C_{max} , AUC) is less than that in humans at the maximum recommended human dose (MRHD) of 1200 mg/day.

Oral administration of eslicarbazepine acetate (40, 160, 320 mg/kg/day) to pregnant rabbits throughout organogenesis resulted in fetal growth retardation and increased incidences of skeletal variations at the mid and high doses. The no-effect dose (40 mg/kg/day) is less than the MRHD on a mg/m² basis.

Oral administration to pregnant rats (65, 125, 250 mg/kg/day) throughout organogenesis resulted in embryolethality at all doses, increased incidences of skeletal variations at the mid and high doses, and fetal growth retardation at the high dose. The lowest dose tested (65 mg/kg/day) is less than the MRHD on a mg/m² basis.

When eslicarbazepine acetate was orally administered to female mice during pregnancy and lactation (150, 350, 650 mg/kg/day), the gestation period was prolonged at the highest dose tested. In offspring, a persistent reduction in offspring body weight and delayed physical development and sexual maturation were observed and the mid and high doses. The lowest dose tested (150 mg/kg/day) is less than the MRHD on a mg/m² basis.

When eslicarbazepine acetate was orally administered (65, 125, 250 mg/kg/day) to rats during pregnancy and

lactation, reduced offspring body weight was seen at the mid and high doses. Delayed sexual maturation and a neurological deficit (decreased motor coordination) were observed at the highest dose tested. The no-effect dose for adverse developmental effects (65 mg/kg/day) is less than the MRHD on a mg/m² basis.

The rat data are of uncertain relevance to humans because of differences in metabolic profile between species.

Pregnancy Registry

Physicians are advised to recommend that pregnant patients taking APTIOM enroll in the North American Antiepileptic Drug Pregnancy Registry. This can be done by calling 1-888-233-2334 (toll-free), and must be done by patients themselves. Information on the registry can also be found at the website <http://www.aedpregnancyregistry.org/>.

Nursing Mothers

Eslicarbazepine is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from APTIOM, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in patients below 18 years of age have not been established.

In a juvenile animal study in which eslicarbazepine acetate (40, 60, 160 mg/kg/day) was orally administered to young dogs for 10 months starting on postnatal day 21, mortality and evidence of immunotoxicity (bone marrow hypocellularity and lymphoid tissue depletion) were observed at all doses. Convulsions were seen at the highest dose tested. Adverse effects on bone growth (decreased bone mineral content and density) were seen in females at all doses at the end of the dosing period, but not at the end of a 2-month recovery period. None of these findings were reported in adult dogs dosed with eslicarbazepine acetate for up to 12 months in duration. A no-effect dose for adverse effects on juvenile dogs was not identified.

Geriatric Use

There were insufficient numbers of patients ≥65 years old enrolled in the controlled epilepsy trials (N=15) to determine the efficacy of APTIOM in this patient population. The pharmacokinetics of APTIOM were evaluated in elderly healthy subjects (N=12). Although the pharmacokinetics of eslicarbazepine are not affected by age independently, dose selection should take in consideration the greater frequency of renal impairment and other concomitant medical conditions and drug therapies in the elderly patient. Dose adjustment is necessary if CrCl is <50 mL/min.

Patients with Renal Impairment

Clearance of eslicarbazepine is decreased in patients with impaired renal function and is correlated with creatinine clearance. Dosage adjustment is necessary in patients with CrCl<50 mL/min.

Patients with Hepatic Impairment

Dose adjustments are not required in patients with mild to moderate hepatic impairment. Use of APTIOM in patients with severe hepatic impairment has not been evaluated, and use in these patients is not recommended.

DRUG ABUSE AND DEPENDENCE

Controlled Substance

APTIOM is not a controlled substance.

Abuse

Prescription drug abuse is the intentional non-therapeutic use of a drug, even once, for its rewarding psychological or physiological effects. Drug addiction, which develops after repeated drug abuse, is characterized by a strong desire to take a drug despite harmful consequences, difficulty in controlling its use, giving a higher priority to drug use than to obligations, increased tolerance, and sometimes physical withdrawal. Drug abuse and drug addiction are separate and distinct from

physical dependence (for example, abuse may not be accompanied by physical dependence).

In a human abuse study in recreational sedative abusers APTIOM showed no evidence of abuse. In Phase 1, 1.5% of the healthy volunteers taking APTIOM reported euphoria compared to 0.4% taking placebo.

Dependence

Physical dependence is characterized by withdrawal symptoms after abrupt discontinuation or a significant dose reduction of a drug.

The potential for APTIOM to produce withdrawal symptoms has not been adequately evaluated. In general, antiepileptic drugs should not be abruptly discontinued in patients with epilepsy because of the risk of increased seizure frequency and status epilepticus.

OVERDOSAGE

Signs, Symptoms, and Laboratory Findings of Acute Overdose in Humans

Symptoms of overdose are consistent with the known adverse reactions of APTIOM and include hyponatremia (sometimes severe), dizziness, nausea, vomiting, somnolence, euphoria, oral paraesthesia, ataxia, walking difficulties, and diplopia.

Treatment or Management of Overdose

There is no specific antidote for overdose with APTIOM. Symptomatic and supportive treatment should be administered as appropriate. Removal of the drug by gastric lavage and/or inactivation by administering activated charcoal should be considered.

Standard hemodialysis procedures result in partial clearance of APTIOM. Hemodialysis may be considered based on the patient's clinical state or in patients with significant renal impairment.

PATIENT COUNSELING INFORMATION

See FDA-approved Medication Guide and Patient Counseling Information section in the Full Prescribing Information.



Manufactured for:
Sunovion Pharmaceuticals Inc.
Marlborough, MA 01752 USA

Under license from

* is a registered trademark of Dainippon Sumitomo Pharma Co., Ltd. Sunovion Pharmaceuticals Inc., is a U.S. subsidiary of Dainippon Sumitomo Pharma Co., Ltd.

© 2014 Sunovion Pharmaceuticals Inc.
All rights reserved.

November 2013
2/14 APT080-14